Keeping up with the immunization schedule: Meningococcal and More

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Faculty/Presenter Disclosure

- **Faculty:** Dr. Dat Tran

- **Relationships with commercial interests:**
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  - GSK via CPS
  - Hoffman La Roche
  - Sanofi Pasteur via Clinical Trials Research Center/Canadian Center for Vaccinology
  - **Speakers Bureau/Honoraria:** Not applicable
  - **Consulting Fees:** Not applicable
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• Potential for conflict(s) of interest:
  – Dr. Dat Tran has received an honorarium from Peel Public Health.
Mitigating Potential Bias

- Any recommendations made are those of the National Advisory Committee on Immunization (NACI) and the Provincial Infectious Diseases Advisory Committee (PIDAC).
Objectives

• Describe the indications, effectiveness and side effects of pediatric meningococcal vaccines (Men-C-C, Men-C-ACYW-135, 4CMenB).
• Understand the process and importance of reporting adverse events following immunization.
• Effectively interpret and execute an immunization catch-up schedule (small group case scenarios).
Princeton starts mass meningitis B vaccinations
7 students stricken by disease

Novartis submits meningitis B vaccine for FDA approval
Swiss drugmaker Novartis said on Tuesday it had submitted its meningitis B vaccine Bexsero for adolescents and young people to the U.S. Food and Drug Administration (FDA) for marketing approval.

16-year-old in Quebec dies after contracting Meningitis Type B
The Montérégie public health board has confirmed that there is no large-scale vaccination planned after a 16-year-old boy died of Meningitis Type B in September.
GLOBALNEWS.CA  |  BY ANNE LECLAIR

 Acadia University students line up for meningitis vaccinations
Clinic set up at the Fountain Commons on Wolfville campus

Targeted Meningococcal Serogroup B Vaccination Campaign in the Saguenay–Lac-Saint-Jean Region
11.5 v 2.1/100,000 clone ST-269
Invasive Meningococcal Disease

- *N. meningitidis*: encapsulated GN diplococcus
- Strictly human pathogen
- Asymptomatic carriage common
  - <1% of carriers become symptomatic
- Transmission
  - Droplet
  - Direct contact
  - Incubation period: 2-10 days (usually 3-4 days)
  - 24 hrs post antibiotic treatment

Multiple Choice

What proportion of the population are nasopharyngeal carriers of *N. meningitidis*?

A) 5%
B) 10%
C) 15%
D) 20%
Clinical Presentation

Lower extremities showing meningococcemia

Early Rash

Advanced Rash

Sources: American Academy of Pediatrics © 2011
Meningitis Research Foundation of Canada
http://www.meningitis.ca/en/MeningococcalDisease
Death and Sequelae Among Survivors* of Serogroup C Meningococcal Disease
Quebec, Canada, 1990–1994

*Average age of patients was 17.6 years (median, 14 years).
†Some patients had multiple sequelae.

Incidence of IMD by serogroup, IMPACT 2002-2009

2002 – 2005: implementation of MenC immunization programs

Source: Bettinger et al. (2012) Pediatr Infect Dis J
Incidence of serogroup B by age, IMPACT 2002-2009

Source: Bettinger et al. (2012) Pediatr Infect Dis J
MENINGOCOCCAL VACCINES
# The serogroup B challenge

<table>
<thead>
<tr>
<th>Polysaccharide capsule</th>
<th>OMV (protein-based)</th>
<th>Subcapsular antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Structurally homologous to surface of human neuronal cells</td>
<td>• Immunogenic &amp; effective for a single serogroup B strain</td>
<td>• Multiple components</td>
</tr>
<tr>
<td>➔ Poorly immunogenic</td>
<td>• &gt;8000 MenB strains exist</td>
<td>• Surface exposed</td>
</tr>
<tr>
<td>➔ Potential induction of autoimmune response</td>
<td></td>
<td>• Highly conserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Induce bactericidal activity</td>
</tr>
</tbody>
</table>

- **Capsular polysaccharide (self antigen)**

4CMen B Vaccine

• First vaccine developed using antigen mining and reverse vaccinology; 75% of antigens are novel

• May have effectiveness across multiple serogroups and clonal complexes that includes antigens from other Neisseria species

• Uncertainty about its effectiveness and capacity to interrupt circulation of bacteria and sustain herd immunity

• Is not authorized for adult use in Canada
## Vaccine effectiveness (VE)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysaccharide vaccine MPSV4 (Menomune) &gt;55 yrs</td>
<td>Less effective than conjugate vaccines; conjugate vaccines are preferred</td>
</tr>
<tr>
<td>Conjugate vaccines</td>
<td>Men-C-C VE in infants 97% within one year of vaccination, decreasing to 68% after 1 year. <strong>Longer term vaccine effectiveness requires receipt of a booster dose in the second year of life (≥1 year)</strong> for those immunized in infancy.</td>
</tr>
<tr>
<td></td>
<td>Menactra VE in adolescence is 80% to 85%</td>
</tr>
<tr>
<td></td>
<td>Menveo more immunogenic in children &lt; 2 yrs</td>
</tr>
<tr>
<td></td>
<td>Nimerix immunogenicity &amp; safety comparable to Men-C-C</td>
</tr>
<tr>
<td>Meningococcal Serogroup B (4CMenB) vaccine</td>
<td>Immunogenic vaccine, although its effectiveness, impact on carriage and duration of protection are unknown or data limited</td>
</tr>
<tr>
<td></td>
<td>Covers ~66% of meningococcal B strains in Canada</td>
</tr>
</tbody>
</table>
Contraindications

- History of anaphylaxis after previous administration of the vaccine
- Persons with proven immediate or anaphylactic hypersensitivity to any component of the vaccine or its container

For meningococcal vaccines, potential allergens include:

- **Menactra®**: diphtheria toxoid protein
- **Meningitec®**: latex in vial stopper, diphtheria CRM197 toxoid carrier protein
- **Menjugate®**: latex in tip cap of syringe, diphtheria CRM197 toxoid carrier protein
- **Menomune®**: thimerosal, latex
- **Menveo™**: diphtheria CRM197 toxoid carrier protein
- **NeisVac-C®**: tetanus toxoid protein
- **Bexsero**: latex in the tip cap of the syringe, kanamycin
Side effect profile

For all meningococcal vaccines:

- Local inj’n site rxn, headache, fever, malaise
- Severe reactions are rare

For 4CMenB vaccine:

- **Fever** is a common side effect. NACI recommends considering using routine prophylactic administration of acetaminophen and/or separating administration of 4CMenB vaccine from other immunizations to prevent fever in infants/children up to 3 years of age

- Other side effects include: skin rash, vomiting, diarrhea, painful muscles/joints
What is Publicly Funded in Ontario?

- **Menjugate** (Men-C-C) at 12 months

- **Menactra** (Men-C-ACYW135) in grade 7 school clinics

- **High Risk Individuals and Close Contacts**
  - Men-C-ACYW-135 (Menactra) 9 months-55 years
    - N.B. NACI preferential recommendation of Menveo for high risk children < 2 yrs
  - Men-P-ACYW-135 (Menomune) ≥ 55 years
  - 4CMenB (Bexsero) 2 months – 17 years of age
What about Men B?

NACI recommends...

Individuals ≥ 2 months of age:

- **High risk of meningococcal disease** (publicly funded 2 months-17 yrs)
- **Close contacts** (publicly funded 2 months-17 yrs)
- **Who are without contraindications to the vaccine and who wish to be immunized**
Meningococcal High Risk Eligibility Criteria

- Functional or anatomic asplenia
- Complement, properdin, factor D deficiency or primary antibody deficiencies
- Cochlear implant recipients (pre/post implants)
- Acquired complement deficiency
- HIV
When will 4CMenB vaccine be publicly funded for general population?
What are my obligations to recommend a vaccine that is not publicly funded?

https://www.cmpa-acpm.ca/-/new-vaccines-what-are-your-obligations
Meningococcal immunization schedule for individuals at high risk of IMD

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended vaccine</th>
<th>Schedule</th>
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<tr>
<td>2-11 months of age</td>
<td>Menveo™</td>
<td>2-3 doses given at least 8 weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
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<td>1 dose between 12 -23 months of age (at least 8 weeks after the last dose)</td>
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<tr>
<td>24 months and older</td>
<td>Men-C-ACYW-135 (Menactra® or</td>
<td>2 doses at least 8 weeks apart</td>
</tr>
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<td>Menveo™) (off-label for &gt;55 yrs)</td>
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*Refer to the MOHLTC handout for the 4CMenB high risk schedule*

Booster requirements individuals at high risk

Men-C-ACYW-135

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<th>Age of vaccination</th>
<th>Booster schedule (if at continued risk)</th>
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<tr>
<td>6 years and younger</td>
<td>Every 3-5 years</td>
</tr>
<tr>
<td>7 years and older</td>
<td>Every 5 years</td>
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4CMenB: Data on duration of immunity is limited. The need for a booster dose is yet to be determined.

Persistence of specific bactericidal antibodies at 5 years of age after vaccination against serogroup B meningococcus in infancy and at 40 months

Fiona McQuaid MBBS, Matthew D. Snape MBBS MD, Tessa M. John BSc, Sarah Kelly MSc, Hannah Robinson RN, Ly-Mee Yu MSc, Daniela Toneatto MD, Diego D’Agostino MSc, Peter M. Dull MD, Andrew J. Pollard PhD

CMAJ, April 21, 2015, 187(7)
Which meningococcal vaccines should I prescribe for travel?

Cases of IMD in Europe after the 2000 Hajj outbreak of W-135
High risk areas for IMD

- Saudi Arabia (proof of Men-C-ACYW-135 for pilgrims to the Hajj or Umrah in Mecca)
- African meningitis belt
# Meningococcal immunization schedule for travellers

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# Booster requirements travellers

## Men-C-ACYW-135

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*NOTE: Travellers to the Hajj may require more frequent re-vaccination for visa requirements*
Multiple Choice

Your patient is a 17 year old male who is asplenic – which meningococcal vaccine(s) are indicated?

A) Menomune (Men-P-ACYW135) and Bexsero (Men B)
B) Menjugate (Men C) and Bexsero (Men B)
C) Menjugate (Men C) and Menactra (Men –C-ACYW-135)
D) Menactra (Men-C-ACYW-135) and and Bexsero (Men B)
Your 7 year old patient received 3 doses of Menjugate at 2, 4 and 6 months when she lived in Alberta. A letter from Peel Public Health indicates she requires vaccine for meningococcal disease. Why and does she require an additional dose(s)?

A) If given as an infant series, still require a Men-C-C booster dose between 12-23 months for longer duration of immunity.

B) If the booster dose is missed, it needs to be administered for school immunization requirements to attend school.

C) Child will require a dose of Menactra (given in school) once in grade 7.

D) All of the above.
Vaccine Safety

Why would parents want their children to be naturally infected...

"We felt that natural immunity to interceptions would protect us."

The science is clear: The earth is round, the sky is blue, and #vaccineswork. Let's protect all our kids. #GrandmothersKnowBest

when the evidence on vaccine safety and effectiveness is so clear?
By the numbers: 2013*

8.2 million
Approximate number of publicly funded vaccine doses distributed in Ontario

642 adverse events following immunizations reported

Most reported events were mild
- 263 sore arms
- 146 rashes
- 58 fevers

Serious events after vaccines are very rare.
- 27 serious events were reported, which represents:
  - 3.3 in every 1 million doses distributed

Vaccines protect us from serious diseases and save lives.
The risk of serious effects from vaccines is very small compared to the risk of the diseases they prevent.
Health care providers play a vital role in keeping vaccines safe by reporting adverse events after immunization and communicating the benefits of vaccines to their patients.

For all AEFI inquiries, including questions about the form or determining if an AEFI should be reported, contact your local public health unit.
www.publichealthontario.ca
What is an adverse event?

• AEFI = Adverse Event Following Immunization

• Unexpected events that are not listed in the product monograph should be reported.

• Expected events such as vaccination site reactions and fever need not be reported unless more severe/frequent.
Key criteria for reporting an AEFI

• Temporal association, and

• Suspicion that the vaccine or immunization may have caused the event.
Why should an adverse event be reported at all?

• To detect potential signals of adverse reactions not seen in clinical studies

• Particularly important for rare adverse events.

• Physicians are required to report.
Suspension of Rotavirus Vaccine After Reports of Intussusception — United States, 1999

Q: What was RotaShield®?
A: RotaShield® vaccine was the first vaccine to prevent rotavirus gastroenteritis approved for use in the United States in August 1998. For more information about rotavirus, see Question & Answers about Rotavirus.

Q: Did RotaShield® vaccine cause intussusception?
A: In the United States, some infants developed intussusception (defined below) soon after RotaShield® was licensed in August 1998. At first, it was not clear if the vaccine or some other factor was causing the bowel obstructions. CDC quickly recommended that use of the vaccine be suspended and immediately started two emergency investigations to find out if receiving RotaShield® vaccine was causing some of the cases of intussusception.

The results of the investigations showed that RotaShield® vaccine caused intussusception in some healthy infants younger than 12 months of age who normally would be at low risk for this condition. The risk of intussusception increased 20 to 30 times over the expected risk for children of this age group within 2 weeks following the first dose of RotaShield® vaccine. The risk increased 3 to 7 times over the expected risk for this age group within two weeks after the second dose of RotaShield® vaccine. There was no increase in the risk of intussusception following the third dose of RotaShield® vaccine, or when three weeks had passed following any dose of the vaccine.

Intussusception from all other causes is most common among infants in the first year of life; 1 child in 2,000 children to 1 child in 3,000 children is affected before one year of age. Based on the results of the investigations, CDC estimated that one or two additional cases of intussusception would be caused among each 10,000 infants vaccinated with RotaShield® vaccine.
4CMenB: Rare adverse events to monitor

1. Febrile convulsions
   - Primary infant series: 0.1 events/1000 vaccinations in 4CMenB study arms (none in control study arms)

2. Severe transient arthralgia
   - 7/84 children aged 40-42 months
   - 2/7 reported arthralgia after both 1st and 2nd vaccination

3. Kawasaki disease
   - 7 cases (6 in vaccine recipients, 1 in control) across all phase 2 and 3 studies
   - Onset 1 day to 5.5 months after vaccination

How to report an AEFI

http://www.peelregion.ca/health/professionals/tools/forms.htm
Vaccine Safety (AEFIs)

Monthly Aggregate count reports and Reporting of admitted cases as they are found of **selected** AEFIs that present with:

- **Neurologic events**
  - Seizures
  - Encephalopathy/itis & ADEM
  - Myelitis
  - GBS and other acute flaccid paralysis
- **Non-neurological events**
  - Thrombocytopenia
  - Intussusception (post rotavirus vaccine)
  - Vasculitides (Kawasaki, HSP and others)
  - Complication of vaccination (non neurological)
  - Other AEFIs (found or called to attention)

- Priority on comprehensive screening of acute neurological admissions
IMPACT: Challenges & Limitations AEFI Surveillance

• Unable to identify recently vaccinated admissions as open-ended target
  – requires immunization documentation (either in hospital chart or from physician or public health records)

• Captures pre-defined AEFIs (though capacity exists to investigate new targets or undefined events)

• Unable to influence care and/or tests so investigation of alternate causes for AEFI is non-uniform
IMPACT: Challenges & Limitations

• Only catches the “tip of the iceberg” – AEFIs severe enough to require hospital admission

• Vaccine history in chart usually incomplete
  – Requires further searching for information – no existing national registry
References


Ontario Ministry of Health and Long-Term (2014). Provider Fact Sheets


Public Health Agency of Canada (2013). Update on the use of quadrivalent conjugate meningococcal vaccines

Public Health Agency of Canada (2014). Advice for the use of the multicomponent meningococcal serogroup B (4CMenB) vaccine

Public Health Ontario (2012). Reportable Disease Trends

Public Health Ontario (2014). Reporting and Investigation Forms
http://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/Pages/Immunization-Resources.aspx
Acknowledgements

- Julie Bettinger (CFRI) and Heather Samson (IWK) for slides of IMPACT data